ADVERSE DRUG REACTION

Fat necrosis associated with the subcutaneous injection of enoxaparin

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The use of low molecular weight heparins in the prophylaxis of deep vein thrombosis is becoming well established. These agents may offer less risk of unwanted effects such as haemorrhage and heparin induced thrombocytopenia. One of the less recognised complications of subcutaneous injection of any unfractionated or low molecular weight heparin is necrosis of the skin and subcutaneous tissues. This is reputedly less common with the unfractionated heparins. We present a case of fat necrosis following the use of enoxaparin (Clexane) in venous thromboprophylaxis.

Case report

A 79 year old woman sustained a fractured neck of femur, which was fixed with a dynamic hip screw. As standard prophylaxis against deep vein thrombosis, she received enoxaparin 20 mg subcutaneously once daily. On the 12th postoperative day she was noted to have an area of inflammation across the lower abdomen. She was pyrexial but not otherwise unwell. Oral cephadrine and metronidazole were started and the enoxaparin was omitted on the following day. The enoxaparin injections were then restarted in the upper arms. Over the following four days she had increasing discomfort at the site of the rash in her abdomen, where the skin had become tender and indurated despite the antibiotics. A diagnosis of necrotising fasciitis was considered, and a surgical opinion sought.

On examination, the rash comprised a tender indurated band of erythema and purple discolouration measuring approximately 50 × 15 cm across the central abdominal wall, surrounding small patches of devitalised skin. The patient remained well systemically. Intravenous antibiotic treatment with flucloxacillin, benzylpenicillin, and metronidazole was started, and the enoxaparin was stopped. The platelet count was $927 \times 10^9/l$ ($267 \times 10^9/l$ on admission) and the white cell count remained normal.

She underwent surgical debridement of the anterior abdominal wall the same evening. An infraumbilical ellipse of skin and subcutaneous tissue measuring 60 × 20 cm was excised, including all areas of frankly necrotic and devitalised fat and skin. The necrotic process was seen to be localised to the skin and subcutaneous tissues and did not extend to involve the deep fascia. A second area of necrotic fat and skin measuring 10 × 5 cm was excised from the left upper quadrant. Both wounds were loosely packed with proflavine soaked ribbon gauze,

and loose mattress sutures were placed for delayed primary wound closure.

Microscopic examination of the excised abdominal tissue with Gram staining showed a heavy neutrophil infiltrate but no organisms. There was no bacterial growth on direct culture, but on enrichment culture *Enterococcus gallinarum* group D was isolated. Intravenous augmentin, to which the organism was sensitive, was begun. Histological examination showed non-specific inflammatory changes with abscess formation.

The patient made an uneventful recovery from surgery. All the abdominal wounds healed satisfactorily, and she was discharged home on the 14th postoperative day.

Discussion

O'Toole was the first to report cutaneous complications at the site of subcutaneous heparin injection in 1973.¹ Since then there have been sporadic case reports of reactions at both localised² and distant sites.³ The first report of subcutaneous necrosis with low molecular weight heparin was by Manoharan in 1992,⁴ following the injection of dalteparin (Fragmin) in a patient with documented sensitivity to unfractionated heparin. A skin reaction induced by enoxaparin was first reported by Phillips *et al* in 1993,⁵ in a patient also shown to be sensitive to unfractionated heparin and dalteparin. At the time of writing, the Committee on Safety of Medicines (CSM) and Medicines Control Agency have received a single report of injection site necrosis associated with enoxaparin (CSM, personal communication).

The pathogenesis of the condition remains unclear. A delayed hypersensitivity reaction of the Arthus type is possible, although an alternative mechanism is heparin dependent platelet activating IgG, causing platelet aggregation and thrombosis. There appears to be a delay in the development of the symptoms and signs of cutaneous and subcutaneous necrosis following injection. This latent period can last for up to two weeks, and as there is also an interval of several hours before other lesions develop following further injections, there is potential for diagnostic confusion. The reaction appears to be caused directly by the heparin or the low molecular weight fraction rather than by a carrier compound, as neither enoxaparin nor dalteparin preparations, nor many of the available heparin preparations, contain preservatives.

This case highlights the potential risk of skin necrosis with subcutaneous enoxaparin injection.

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tions. The rarity of this complication, combined with the latency between injection and clinical manifestations, may lead to delay in diagnosis. The condition may rapidly progress from mild erythema to skin and subcutaneous tissue necrosis despite antibiotics. Wide surgical debridement may be required, although conservative management has been successful in less extensive cases.⁶ In this case *Enterococcus gallinarum* group D was isolated on enrichment cultures. Previous reports have not identified an infective element in the development of necrosis.

Thrombocytopenia has been reported in some cases,⁷ and it has been suggested that the lesions are associated with heparin induced platelet aggregation. Indeed, recognition of thrombocytopenia may alert the physician to the possible development of skin necrosis.⁸ However, thrombocytopenia appears to be uncommon with low molecular weight heparins,⁹ and it is not a feature of all cutaneous reactions to heparin.¹⁰ In our case, not only did necrosis occur without thrombocytopenia, but there was even a marked increase in the platelet count. This suggests that the pathogenesis of the condition is not directly related to the effects of heparin dependent platelet activating globulin and another explanation should be sought.

Summary points

- Fat necrosis is a rare complication of low molecular weight heparin injections, including enoxaparin.
- The latency of the clinical manifestation may delay diagnosis.
- Pathogenesis is unknown.
- Necrosis can occur without thrombocytopenia.

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Medical Anniversary

Theodor Billroth, 29 January 1881

Theodor Billroth (1829–1894) was born in Bergen on the island of Ruegen in the Baltic Sea, son of a minister. He was educated at Gottingen and became professor of surgery at Zurich (1860–67) and Vienna (1867–94). He founded the Vienna School of Surgery.

He performed the first successful gastrectomy for carcinoma of the stomach on Theresa Heller on this day in Vienna. He had also performed the first successful oesophagectomy (1872) and laryngectomy (1873).

He was a close friend of Brahms and was himself a fine musician.—*D G James*